Attorney Docket No.: **RTS-0333**
Inventors: **Bennett and Dobie**
Serial No.: **10/008,789**
Filing Date: **November 8, 2001**
Page 5

REMARKS

Claims 1, 2 and 4-20 are pending in the instant application. Claims 1, 2 and 4-20 have been rejected. Claims 11 and 16-18 have been canceled. Claims 1 and 15 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 15-20 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification is enabling for compounds 8 to 50 nucleobases in length that hybridize with and inhibit the expression of thyroid hormone receptor interactor 6 *in vitro*, but the Examiner then suggests that the specification as filed is not enabling for *in vivo* uses of the claimed antisense compounds. The Examiner cites several articles on the technology of antisense to support the position regarding

extrapolation to *in vivo* uses. Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully point out that claims 19 and 20 are not method claims as suggested by the Examiner. These claims are composition claims that further define the compounds of claim 1. Therefore, these claims are not properly rejected under 35 U.S.C. 112, first paragraph for the reasons stated by the Examiner. Accordingly, Applicants are not addressing the rejection of these claims in the following comments.

Applicants disagree with the Examiner's suggestion that the cited references support the position that application of antisense *in vivo* as a pharmaceutical is unpredictable.

The Examiner has pointed to two articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Jen and Gewirtz (2000) is a review paper on the evolution of technology to suppress gene expression, including

antisense technology, and its use in human disease. Nowhere does this paper teach or suggest that antisense compounds identified from well-designed *in vitro* studies would be inherently unpredictable when used *in vivo*.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

In an earnest effort to advance the prosecution of this case, Applicants have amended claim 15 and canceled claims 16-18, with Applicants reserving the right to file a continuing application directed to this subject matter. Therefore, withdrawal of the rejection is requested.

II. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1, 2 and 11 have been rejected under 35 U.S.C. 102(b) as being anticipated by Schneider (2001). The Examiner suggests that this paper discloses the reduction of endogenous thyroid hormone receptor interactor 6 protein by antisense technologies and a reverse PCR primer 27 nucleobases in length. The Examiner

further suggests that since this oligonucleotide is 100% complementary to thyroid hormone receptor interactor 6 it is assumed to inherently possess antisense activity. Applicants respectfully traverse this rejection.

At the outset, claim 11 has been canceled and claim 1, and by dependency claim 2, have been amended to recite that the antisense compounds of the instant invention are targeted to specific regions within the sequence of thyroid hormone receptor interactor 6 of SEQ ID NO: 3. Support for these amendments to the claims can be found throughout the specification as filed but in particular at pages 80-84.

Schneider (2001) is a German article and only the English translation of the abstract was provided by the Examiner. The reference published on August 6, 2001. In this abstract, the authors mention that antisense techniques were used to decrease levels of thyroid hormone receptor interactor 6 protein in cells. Only one 27-mer reverse primer is disclosed and this compound is targeted to the stop codon. Nowhere does this abstract teach or suggest antisense compounds as now claimed which are targeted to specific regions or active sites of SEQ ID NO: 3. In order to anticipate an invention the cited art must teach each and every limitation of the claims (MPEP 2131). Accordingly, this reference

fails to anticipate the claims as amended. Withdrawal of this rejection is therefore respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider (2001), in view of Baracchini et al. (US Patent 5,801,154) and Fritz et al. (1997). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill to make antisense oligonucleotides encoding thyroid hormone receptor interactor 6 because it was known in the art that is was of interest to investigate this protein in human cancers (Yi and Beckerle). The Examiner suggests that a reasonable expectation of success is provided by the teachings of Schneider and Baracchini et al., while the motivation to modify the compounds is provided by the teachings of Baracchini et al. and Fritz et al. Applicants respectfully traverse this rejection.

As discussed *supra*, Applicants have amended the claims to recite specific regions within SEQ ID NO: 3 that are targeted by antisense compounds. These regions are taught in the specification as filed.

Schneider et al. (2001), as discussed *supra*, disclose the general use of antisense for inhibition of expression of thyroid hormone receptor interactor 6 and one 27 mer compound. Nowhere does this paper, from the translation provided, teach or suggest regions or active sites of thyroid hormone receptor interactor 6 that might be targeted specifically with antisense. It is only with the specification in hand that one of skill has evidence that antisense inhibition of thyroid hormone receptor interceptor 6 could be successfully inhibited by compounds that target particular regions or active sites of SEQ ID NO: 3.

The secondary references cited fail to overcome the deficiencies in the teachings of this primary reference.

The '154 patent teaches modification to antisense oligonucleotides in general as a way to enhance activity. However, this general discussion of modified oligonucleotides does not teach or suggest use of antisense compounds of any type to target specific regions or active sites of thyroid hormone receptor interactor 6 of SEQ ID NO: 3 and the successful inhibition of expression using antisense.

Fritz et al. (1997) disclose the use of cationic polystyrene nanoparticles as carrier systems for antisense compounds in general. However, this general discussion of carrier systems for

oligonucleotides does not teach or suggest use of antisense compounds of any type to target specific regions or active sites of thyroid hormone receptor interactor 6 of SEQ ID NO: 3 and the successful inhibition of expression using antisense.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Mere teaching of the function of a gene and/or its protein product and then teaching of antisense technology in general does not provide one of skill with the expectation of success in developing antisense targeted to specific regions of a gene. Further, the claims, as amended, which recite specific regions or active sites within thyroid hormone receptor interactor 6 of SEQ ID NO: 3, are not taught or suggested by any of the references individually or when combined. Therefore, the limitations of the claims as amended clearly are not taught or suggested by the combination of prior art references, nor is any expectation of successful use of such antisense compounds provided by the combination of prior art.

Thus, the combination of prior art cited cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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Date: March 10, 2003

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